Drug Class Review
on
Nasal Corticosteroids

Update #2: Preliminary Scan Report #2

November 2010

The Agency for Healthcare Research and Quality has not yet seen or approved this report

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OBJECTIVE:

The purpose of this preliminary updated literature scan process is to provide the Washington State Health Care Authority with a preview of the volume and nature of new research that has emerged subsequent to the previous scan. Provision of the new research presented in this report is meant only to assist with Washington State Health Care Authority's consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Washington State Health Care Authority ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the FDA or Health Canada since the last report. Other important studies could exist.

Date of Last Update:

Update #1 Final Report was completed in June 2008.

Date of Last Update Scans:

Scan #1 was completed in July 2009

Scope and Key Questions

Report authors drafted preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. For the Original Report and for Update #1, these were reviewed and revised by the Washington State Preferred Drug Program (PDP). Washington State PDP was responsible for ensuring that the scope of the review reflected the populations, drugs, and outcome measures of interest to both clinicians and patients. The Washington State PDP approved the following key questions to guide this review:

1. For adults and children with seasonal or perennial (allergic and non-allergic) rhinitis, do nasal corticosteroids differ in effectiveness?

2. For adults and children with seasonal or perennial (allergic and non-allergic) rhinitis, do nasal corticosteroids differ in safety or adverse events?

3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or comorbidities, or in pregnancy and lactation for which one nasal corticosteroid is more effective or associated with fewer adverse events?

Inclusion Criteria

Population(s)

Adult patients and children (under age 18) in outpatient settings with the following diagnosis:

- Seasonal or perennial allergic or non-allergic rhinitis

Table 1. Interventions

Generic name	Trade name(s)	Forms
Beclomethasone	Beconase®, Beconase AQ®, Vancenase®, Vancenase AQ®	Nasal spray
Budesonide	Rhinocort®, Rhinocort Aqua®	Nasal spray
Ciclesonide	Omnaris®	Nasal spray
Flunisolide	Nasalide®, Nasarel®	Nasal spray
Fluticasone furoate	Veramyst®	Nasal spray
Fluticasone propionate[a]	Flonase®	Nasal spray
Mometasone	Nasonex®	Nasal spray
Triamcinolone	Nasacort®, Nasacort AQ®	Nasal spray

[a] Unless otherwise stated, fluticasone propionate is referred to as 'fluticasone' or 'fluticasone aqueous' throughout this report; fluticasone furoate is always referred to as such.

Effectiveness outcomes

- Symptomatic relief
- Onset of action

Safety outcomes

- Overall adverse effect reports
- Withdrawals due to adverse effects
- Serious adverse events reported
- Specific adverse events (localized infection of nasal mucosa, hypersensitivity, hypercorticism, HPA suppression, growth suppression in pediatric population, headache, throat soreness, dry mouth, nasal irritation)

Study designs

1. For efficacy, controlled clinical trials and good-quality systematic reviews
2. For safety, controlled clinical trials and good-quality systematic reviews and observational studies.

METHODS

Literature Search

To identify relevant citations, we searched MEDLINE (July 2009 through October 2010) using terms for included drugs and indications, and limits for humans, English language, and randomized controlled trials or controlled clinical trials. We also searched FDA (http://www.fda.gov/medwatch/safety.htm) and Health Canada (http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2006/index_e.html) websites for identification of new drugs, indications, and safety alerts, as well as, the US Agency for Healthcare Research and Quality, AHRQ, (http://www.ahrq.gov and the Canadian Agency for Drugs and Technologies in Health, CADTH, (http://www.CADTH.ca for recent comparative effectiveness reviews.

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Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

New Drugs

None

New Indications

None

New Safety Alerts

None

New Studies

Searches resulted in 40 citations. Among those, there are 7 new, potentially relevant controlled clinical trials, including 2 head-to-head trials (Appendix A) and 5 placebo-controlled trials (Appendix B). One head-to-head trial compares fluticasone furoate with fluticasone propionate in adults. The other head-to-head trial compares mometasone furoate with beclomethasone dipropionate in children.

The Table 1 below provides a summary of the content of the head-to-head and placebo-controlled trials. The majority of the new trials involve mometasone furoate.

Table 1. New head-to-head and placebo controlled trials for Scan #2

Author Year	NCS	Focus/Notes	Trial Type
Meltzer, 2010	fluticasone furoate vs fluticasone propionate	Adult allergic rhinitis	HTH
Ratner, 2009	mometasone furoate vs beclomethasone dipropionate	PAR in children	HTH
LaForce, 2009	ciclesonide hydrofluoroalkane	SAR in patients 12 and older	PC
Jacobs, 2009	fluticasone furoate	Nasal and ocular symptoms of SAR	PC
Anolik, 2009	mometasone furoate	SAR in adolescents	PC
Meltzer, 2010	mometasone furoate	Allergic rhinitis, rhinitis-disturbed sleep	PC
Prenner, 2010	mometasone furoate	Ocular symptoms of SAR	PC

In addition, there were 14 potentially relevant trials from the previous scan, which included one head-to head trial and 13 placebo-controlled trials. Table 2 below gives the study details from Scan #1.

Table 2. Relevant trials from Scan #1

Author Year	NCS	Focus/Notes	Trial Type
Okubo, 2009	fluticasone furoate vs fluticasone propionate	Adults with allergic rhinitis due to Japanese cedar pollinosis	HTH
Agondi, 2008	beclomethasone	Comorbid asthma in adults	PC
Couroux, 2009	ciclesonide	SAR in adults	PC
Patel, 2008	ciclesonide	SAR in adults	PC
Jacobs, 2009	fluticasone furoate	Non-allergic rhinitis	PC
Nathan, 2008	fluticasone furoate	PAR in adults/adolescents	PC
Vasar, 2008	fluticasone furoate	PAR in adults/adolescents	PC
Okubo, 2008	fluticasone furoate	PAR in adult	PC
Maspero, 2008	fluticasone furoate	PAR in children	PC
Zieglmayer, 2008	fluticasone furoate	SAR in adults	PC
Meltzer, 2009	fluticasone furoate	SAR in children	PC
Andrews, 2009	fluticasone furoate	SAR: night-time symptoms	PC
Pedroletti, 2008	mometasone	PAR and comorbid asthma in children	PC
Weinstein, 2009	triamcinolone	PAR in children	PC

The addition of the studies from Scan #1 to the new studies found in Scan #2, result in 3 total head-to-head trials and 18 total placebo-controlled trials found since the last NCS update.

Comparative Effectiveness Reviews

The search of AHRQ and CADTH websites revealed no comparative effectiveness reviews involving nasal corticosteriods.

APPENDIX A:

Meltzer EO. Andrews C. Journeay GE. Lim J. Prillaman BA. Garris C. Philpot E. (2010). "Comparison of patient preference for sensory attributes of fluticasone furoate or fluticasone propionate in adults with seasonal allergic rhinitis: a randomized, placebo-controlled, double-blind study." Annals of Allergy, Asthma, & Immunology. 104(4):331-8.

BACKGROUND: Intranasal corticosteroids are first-line treatment for moderate-to-severe seasonal allergic rhinitis (AR). OBJECTIVES: To compare preferences for fluticasone furoate and fluticasone propionate nasal sprays after 1 week of treatment in patients with symptomatic seasonal AR. METHODS: Patients with seasonal AR were enrolled (n = 360) and randomized 1:1 to active treatment (fluticasone furoate, 110 microg, or fluticasone propionate, 200 microg, followed by crossover treatment for 1 week each) or matched placebo sequence with a 1-week washout before crossover dosing. Fluticasone furoate and fluticasone propionate efficacy was measured by change from baseline during 1 week in daily reflective total nasal symptom score (rTNSS) that assessed severity of rhinorrhea, nasal congestion, nasal itching, and sneezing. Patient preference for fluticasone furoate or fluticasone propionate was assessed at the end of the study by questionnaire. RESULTS: Three hundred sixty patients from 29 clinical sites in the Unites States were randomized and treated between August 1, 2007 and November 30, 2007. Most patients were white (73%) and female (59%), with a mean age of 38.3 years, and had had seasonal AR for at least 10 years (74%). Fluticasone furoate and fluticasone propionate each reduced the daily rTNSS compared with their respective placebos (least squares mean [SD] difference, -0.8 [0.24], P < .001, and -0.6 [0.24], P = .01, respectively). More patients (P < .001) preferred fluticasone furoate to fluticasone propionate based on attributes of scent or odor (58% vs 27%), aftertaste (60% vs 18%), leaking out of the nose and down the throat (59% vs 21%), and mist gentleness (57% vs 26%). No statistically significant differences were seen in preferences regarding ease of use, delivery method, or device comfort. CONCLUSION: Both fluticasone furoate and fluticasone propionate significantly improved symptoms in adult patients with seasonal AR. Most patients preferred the sensory attributes of fluticasone furoate to those of fluticasone propionate after 1 week of treatment.

Ratner PH. Meltzer EO. Teper A. (2009). "Mometasone furoate nasal spray is safe and effective for 1-year treatment of children with perennial allergic rhinitis." International Journal of Pediatric Otorhinolaryngology. 73(5):651-7.

OBJECTIVE: Perennial allergic rhinitis (PAR) affects children at a young age. Current guidelines recommend intranasal corticosteroids as the first-line treatment in patients with moderate-to-severe or persistent disease or in those who have congestion. In this study, the long-term safety and efficacy of mometasone furoate nasal spray (MFNS) were assessed in children with PAR. METHODS: In this multicenter, active-controlled, evaluator-blind, 12-month study, 255 children aged 6-11 years with a >or=1-year history of PAR were randomized to receive once-daily MFNS 100 microg (n=166) or the active comparator beclomethasone dipropionate (BDP) 168 microg (n=85). Changes from

baseline in overall PAR symptoms and response to treatment were rated at each visit. Cosyntropin stimulation testing, as well as tonometry and slit lamp procedures, were performed. Safety variables were assessed. RESULTS: A total of 137 subjects in the MFNS group and 68 in the BDP group completed treatment. The mean reductions in physician- and subject-rated overall condition of PAR at week 52 were -42.1% and -39.7%, respectively, for MFNS, compared with -44.0% and -39.0%, respectively, for BDP. A total of 94% and 100% of MFNS and BDP subjects, respectively, reported adverse events (AEs), which were mostly mild or moderate. The most frequently reported treatment-related AEs in both groups were epistaxis, headache, and pharyngitis. Response to cosyntropin was normal and no posterior subcapsular cataracts were observed in either group. Although no significant changes in intraocular pressure were observed with MFNS, one subject receiving BDP demonstrated this effect. CONCLUSIONS: Treatment with MFNS 100 microg once daily for 1 year was well tolerated in children 6-11 years old, with negligible systemic exposure and no evidence of suppression of the hypothalamic-pituitary-adrenal axis or ocular changes.

APPENDIX B:

Anolik R. Pearlman D. Teper A. Gates D. (2009). "Mometasone furoate improves nasal and ocular symptoms of seasonal allergic rhinitis in adolescents." Allergy & Asthma Proceedings. 30(4):406-12.

Seasonal allergic rhinitis (SAR) is common in adolescents. However, few studies have investigated the effectiveness of intranasal corticosteroids (INSs) for nasal and ocular symptoms of SAR solely in adolescents. The purpose of this study was to determine the safety and efficacy of the INS mometasone furoate nasal spray (MFNS) in adolescents; a post hoc analysis was conducted of adolescents who had participated in a study with adults. Data were analyzed retrospectively for subjects aged 12-17 years with moderate or severe SAR randomized to mometasone furoate, 200 mcg once daily (n = 86), or placebo (n = 82) for 15 days in a multicenter, double-blind, placebo-controlled study. Symptom scores (0 = none to 3 = severe) were recorded in diaries twice daily. End points included changes from baseline in total nasal symptom score (TNSS), individual nasal symptom score (rhinorrhea, congestion, itching, and sneezing), and total ocular symptom score (TOSS). Over 15 days, a significantly greater decrease from baseline in mean TNSS was observed in subjects receiving mometasone furoate (-2.47; -28.8%) compared with those receiving placebo (-0.9; -9.6%; p < 0.001). Significant improvement versus placebo was seen for each full day of treatment. Mometasone furoate significantly improved individual nasal symptoms (p < or = 0.03) and TOSS (p = 0.011) versus placebo. The incidence of adverse events was similar for both treatment groups. MFNS, 200 mcg once daily, is an effective and well-tolerated treatment for symptoms of SAR in adolescents.

Jacobs R. Martin B. Hampel F. Toler W. Ellsworth A. Philpot E. (2009). "Effectiveness of fluticasone furoate 110 microg once daily in the treatment of nasal and ocular symptoms of seasonal allergic rhinitis in adults and adolescents sensitized to mountain cedar pollen."Current Medical Research & Opinion. 25(6):1393-401.

BACKGROUND: Fluticasone furoate (FF) is a novel enhanced-affinity corticosteroid for the treatment of allergic rhinitis, delivered by a unique side-actuated device. This study was designed to investigate the efficacy and safety of FF nasal spray (FFNS) 110 microg once daily compared with placebo in adults and adolescents (aged > or =12 years) with seasonal allergic rhinitis (SAR) symptoms caused by mountain cedar (Juniperus ashei) pollen. METHODS: This was a randomized, double-blind, placebo-controlled, parallel-group, phase III study conducted over a 2-week period (between 10 December 2004 and 19 January 2005) at seven study sites, in Austin, Texas, USA, and San Antonio, Texas, two metropolitan cities in the central Texas Hill Country located approximately 80 miles apart. Adult and adolescent patients (aged > or =12 years) with SAR, who were sensitized to mountain cedar (Juniperus ashei) pollen, were randomized to receive either FFNS 110 microg (n = 152) or placebo (n = 150) once daily. Patients rated the severity of each nasal symptom (rhinorrhea, nasal congestion, nasal itching, and sneezing) and ocular symptom (redness, watery eyes, itching and burning) on a 4-point categorical scale (0 = none, 3 = severe) in a reflective and instantaneous manner.

Patients also rated their overall evaluation of response to therapy. TRIAL REGISTRATION: ClinicalTrials.gov Identifier NCT00115622. RESULTS: FFNS significantly improved the nasal symptoms of SAR compared with placebo. The least square (LS) mean difference in the reflective total nasal symptom score (TNSS) was -0.777 (p = 0.003). A significant reduction in morning pre-dose instantaneous TNSS was also observed compared with placebo (LS mean difference -0.902; p < 0.001). Patients receiving FFNS had significantly greater improvements from baseline in reflective total ocular symptom scores (TOSS) than those receiving placebo (LS mean difference -0.546; p = 0.008). Significant improvements in ocular symptoms with FFNS versus placebo were also observed for morning pre-dose instantaneous TOSS (LS mean difference -0.519; p = 0.009). FFNS had a favorable safety and tolerability profile: fewer adverse events occurred with FFNS (22%) than with placebo (29%), and no serious adverse events were observed. CONCLUSIONS: FFNS 110 microg once daily demonstrated efficacy in relieving both the nasal and ocular symptoms of SAR in adult and adolescent patients.

LaForce C. van Bavel J. Meltzer EO. Wingertzahn MA. (2009). "Efficacy and safety of ciclesonide hydrofluoroalkane nasal aerosol once daily for the treatment of seasonal allergic rhinitis." Annals of Allergy, Asthma, & Immunology. 103(2):166-73.

BACKGROUND: Aerosol-based corticosteroid nasal formulations may be preferred over current aqueous nasal sprays by some patients because they traditionally cause less pharyngeal and anterior nose runoff. OBJECTIVE: To determine the optimal dose, safety, and tolerability of ciclesonide hydrofluoroalkane nasal aerosol in patients with seasonal allergic rhinitis (SAR). METHODS: Patients 12 years or older with a history of SAR received ciclesonide hydrofluoroalkane nasal aerosol to a total dose of 75, 150, or 300 microg or placebo once daily (half dose per nostril) for 2 weeks. The primary efficacy assessment was patient-reported average morning and evening reflective (24-hour) total nasal symptom scores (rTNSS). Secondary efficacy assessments included patient-reported average morning and evening instantaneous TNSS (iTNSS), patient-reported morning iTNSS, physician-assessed nasal signs and symptom severity, and Rhinoconjunctivitis Quality of Life Questionnaire responses. Safety and tolerability were also assessed. RESULTS: Ciclesonide hydrofluoroalkane nasal aerosol demonstrated a statistically significantly greater reduction from baseline in average morning and evening rTNSS (24-hour) vs placebo, with treatment differences as follows: 0.81 (P = .001; 300 microg), 0.90 (P < .001; 150 microg), and 0.66 (P = .01; 75 microg). Improvements in average morning and evening iTNSS and patient-reported morning iTNSS were also significantly improved regardless of dose (P < or = .003 for all ciclesonide groups vs placebo). The incidence of treatment-related adverse events was low (< 1.6% for all) and similar among groups. CONCLUSIONS: Ciclesonide hydrofluoroalkane nasal aerosol demonstrated statistically significant improvements in SAR symptoms vs placebo. On the basis of comparable efficacy and safety profiles observed for all doses, these results suggest that the 75-microg and 150-microg doses of ciclesonide hydrofluoroalkane appear appropriate for further evaluation of efficacy.

Meltzer EO. Munafo DA. Chung W. Gopalan G. Varghese ST. (2010). "Intranasal mometasone furoate therapy for allergic rhinitis symptoms and rhinitis-disturbed sleep." Annals of Allergy, Asthma, & Immunology. 105(1):65-74.

BACKGROUND: Allergic rhinitis (AR) and related nasal congestion cause rhinitis-disturbed sleep (RDS). Intranasal corticosteroids reduce nasal congestion and improve sleep quality in AR but have not been extensively studied in RDS. OBJECTIVE: To evaluate the efficacy of mometasone furoate nasal spray (NS) on nasal symptoms, nasal patency, sleep variables, quality of life, and daytime functioning in perennial AR (PAR) and concomitant RDS. METHODS: In this double-blind 4-week study, 30 adults with PAR and moderate RDS were randomized 2:1 to receive mometasone furoate NS, 200 microg, or placebo each morning. The primary end point was the apnea-hypopnea index. Secondary outcome measures included changes in total nasal symptom score (TNSS), nighttime symptom score, daytime peak nasal inspiratory flow, nighttime flow limitation index, Rhinoconjunctivitis Quality of Life Questionnaire-Standardized (RQLQ-S) score, Epworth Sleepiness Scale score, and Work Productivity and Activities Impairment-Allergy Specific (WPAI-AS) questionnaire score. Analysis of covariance was used for all efficacy end points. RESULTS: The apnea-hypopnea index at study end was not statistically significantly different between groups. However, mometasone furoate NS therapy significantly improved morning (P = .04) and evening (P = .01) TNSSs, morning (P = .049) and evening (P = .03) nasal obstruction/blockage/congestion, daily peak nasal inspiratory flow (P = .03), flow limitation index (P = .02), Epworth Sleepiness Scale score (P = .048), RQLQ-S score (P = .03), and 2 of 5 WPAI-AS domains. Among patients receiving mometasone furoate NS, TNSS improvements were significantly correlated with improved work- and non-work-related productivity. CONCLUSIONS: In patients with PAR and RDS, mometasone furoate NS use improved nasal symptoms, sleepiness, and impairment in daily activities. Correlated reduced nasal symptoms and improved performance suggest that improving AR symptoms with mometasone furoate NS administration can benefit sleep and daytime functioning.

Prenner BM. Lanier BQ. Bernstein DI. Shekar T. Teper A. (2010) "Mometasone furoate nasal spray reduces the ocular symptoms of seasonal allergic rhinitis." Journal of Allergy & Clinical Immunology. 125(6):1247-1253.

BACKGROUND: Mometasone furoate nasal spray (MFNS), a potent intranasal corticosteroid with proved efficacy in relieving nasal allergic rhinitis symptoms, has demonstrated effectiveness in improving ocular symptoms associated with seasonal allergic rhinitis (SAR) in retrospective analyses. OBJECTIVE: We sought to evaluate prospectively the efficacy of MFNS in reducing total ocular symptom scores (TOSSs) and individual ocular symptoms in subjects with SAR. METHODS: Subjects 12 years or older (n = 429) with moderate-to-severe baseline symptoms were randomized to MFNS, 200 microg once daily, or placebo in this 15-day, double-blind, parallel-group study. Subjects evaluated morning instantaneous TOSSs and daily reflective TOSSs, total nasal symptom scores (TNSSs; both instantaneous TNSSs and reflective TNSSs, respectively), and individual ocular and nasal symptoms. Mean changes from baseline averaged over days 2 to 15 (instantaneous) and days 1 to 15 (reflective) were calculated. Quality of life was

assessed by using the Rhinoconjunctivitis Quality of Life Questionnaire. RESULTS: MFNS treatment yielded significant reductions from baseline versus placebo in instantaneous TOSSs (-0.34, P = .026, coprimary end point), instantaneous TNSSs (-0.88, P < .001, coprimary end point), reflective TOSSs (-0.44, P = .005), and reflective TNSSs (-1.06, P < .001). Significant decreases in all individual reflective ocular symptoms and instantaneous eye itching/burning and eye watering/tearing were observed for MFNS versus placebo (P < .05). Numeric improvements in instantaneous eye redness were seen but did not reach statistical significance. Improvements in Rhinoconjunctivitis Quality of Life Questionnaire total scores and individual symptom domains were achieved with MFNS treatment versus placebo (P < .001). MFNS was well tolerated. CONCLUSION: This prospective study demonstrates that MFNS significantly reduces ocular symptoms in subjects with SAR.

Vlckova I. Navratil P. Kana R. Pavlicek P. Chrbolka P. Djupesland PG. (2009). "Effective treatment of mild-to-moderate nasal polyposis with fluticasone delivered by a novel device." Rhinology. 47(4):419-26.

OBJECTIVE: To assess the efficacy and safety of fluticasone propionate administered using OptiNose's novel delivery device (Opt-FP) in subjects with bilateral mild-to-moderate nasal polyposis. METHODS: A prospective, multicentre, randomized, double-blind, placebo-controlled, parallel group study was conducted in adult subjects (n = 109) with mild-to-moderate bilateral nasal polyposis. Subjects received Opt-FP 400 microg or placebo twice daily for 12 weeks. Endpoints included endoscopic assessment of polyp size using Lildholdt's Scale, peak nasal inspiratory flow (PNIF), symptom scores and use of rescue medication. RESULTS: The proportion of subjects with improvement in summed polyp score >or= 1 (Lildholdt\'s Scale) was significantly higher with Opt-FP compared with placebo at 4, 8 and 12 weeks (22% vs 7%, p = 0.011, 43% vs 7%, p < 0.001, 57% vs 9%, p < 0.001). After 12 weeks the summed polyp score was reduced by 35% (-0.98 vs +0.23, p < 0.001). PNIF increased progressively during Opt-FP treatment (p < 0.05). Combined symptom score, nasal blockage, discomfort, rhinitis symptoms and sense of smell were all significantly improved. Rescue medication use was lower (3.1% vs 22.4%, p < 0.001). Opt-FP was well tolerated. CONCLUSIONS: Fluticasone propionate (400 microg b.i.d.) administered using OptiNose's breath actuated bi-directional delivery device was an effective and well tolerated treatment for mild-to- moderate bilateral nasal polyposis.